Number/Name: P-17-0281

[redacted]

SUMMARY INFORMATION

EPA concludes there are human health hazards for the chemical substance based on its estimated physical/chemical properties [poor absorption of the LW fraction based on pchem], by comparing it to structurally analogous chemical substances for which there is information on human health hazard [developmental and reproductive toxicity], and/or other structural information [irritation based on free acid moieties].

Based on the hazard determination and available qualitative and quantative risk information, EPA concludes that there is risk for the PMN substance.

SUMMARY INFORMATION

Human Health Hazard:

- Absorption of the low molecular weight fractions [redacted] is poor all routes (pchem)
- Concern for irritation for the low molecular weight fractions based on [redacted] moieties.
- There is [redacted] residual for a [redacted] compound, and some [redacted] compounds have been shown to induce developmental and reproductive toxicity. Concern for developmental toxicity for the molecular weight species containing [redacted] moieties by uncertain analogy to [redacted]
- There is [redacted] residual [redacted]

Human Health Risk:

- Risks were identified for irritation in workers, which can be mitigated through the use of protective equipment such as impervious gloves, eye protection, and a respirator. The APF of the respirator cannot be determined due to a lack of dose-response for this hazard.
- Risk for systemic toxicity from dermal exposure was identified for workers based on analog data and from [redacted] residual.
- Risk was not identified for systemic toxicity for workers via inhalation exposures.
- Risks were not identified for the general population.

Potentially Useful Information:

Potentially useful information would inform developmental and reproductive toxicity

PART A

SAT Date: 2017-05-02

Health Assessor: Ernest V. Falke

Structure:

PMN: P-17-0281	Submitter: [redacted]			Manu.	Import
Max. PV (KG): [redacted]		Binding Option Marked:		X	
MW: [redacted]	% < 500	[redacted]	% <1000	CASNO [redacted]	

PMN Structure	Prop.	Meas.	Est.
[redacted]	MP		
	BP		>400
	Pres.		at 760 mm Hg
	VP		<0.000001
	S-H2O		<0.000001
	log P		

[redacted]

Analogs:

Analog: [redacted]

USE:

Water-reducible resin [redacted]

This is a polymer exemption (E1).

other_uses

[redacted]

[redacted]

- **Chemical Category:** N/A
- **Chemical Category Health Concerns:**
  - o

- **Category Testing Strategy:**
  -
- **PMN Health Rating:** 1-2

P3B1T1

- **SAT Key Words:**

IRRIT; DEV (UNCERT)

Focus Assessor Comment: Reproductive toxicity will be added as a keyword based on discussion of reproductive findings in the SAT report.

- **Absorption:**

Absorption of the low molecular weight fractions [redacted] is poor all routes(pchem).

Note: Risks were calculated assuming 100% absorption via oral and dermal routes, based on a database of absorption data for other PMN chemicals suggesting underestimation of absorption when based solely on pchem properties.

- **SAT Health Summary:**

Concern for irritation for the low molecular weight fractions based on [redacted] moieties. There is [redacted] residuals for [redacted] compound. Some [redacted] compounds have been shown to induce developmental toxicity. Uncertain concern for developmental toxicity for the molecular weight species containing [redacted] moieties by uncertain analogy to [redacted] No concerns for alkoxysilane moieties because they are not expected to be reactive in this PMN substance.

- **PMN Data:** (study summary, POD)
  -
- **Analog Data:** (analog, structure, study summary, POD)

	[redacted]	[redacted]
Skin/Eye Irritation	Mild skin irritant in rabbits.* Not irritating to rabbit eyes	Slightly irritating to rabbit skin and eyes.
Skin Sensitization	Skin sensitization test on guinea pigs – not conclusive/invalid for lack of positive controls (RAD reviewer).	Skin sensitization test on guinea pigs – negative.
Invitro testing	Gene expression assay (non- guideline assay).** negative for repression of genes relevant to rat testicular malformation. Note- for this assay, pregnant dams were dosed and then RNA was isolated from fetal testes)	Negative in 3 out of 4 in vitro tests for estrogenic activity. **It was positive for receptor activation in an *invitro* test using human osteoblastic (US-O2) reporter gene cell lines for ERα and ERβ).**

Prenatal developmental - Reproductive toxicity in rats	NOAEL Maternal and Developmental Toxicity = 300 mg/kg***, which are based on decreases in body weight, body weight gain, food consumption, gravid uterus weight, and absolute weight gain; decreased fetal body and litter weights, increases in the percentages of small fetuses, increases in the percentage of litters with small fetuses, and increased incidences of incomplete or no ossification.	In a combined oral reproductive/ developmental toxicity screening test (OECD 421), **a NOAEL of 100 mg/kg-day was identified for reproductive toxicity in males based on the decreases in spermatocytes and spermatids in male rats at 300 and 1000 mg/kg-day(males were exposed for 46 days (including mating) and females** from 14 days prior to mating through day 3 of lactation.) Oral developmental toxicity study: A NOAEL of 1050 mg/kg-day for maternal and developmental toxicity in a gestational exposure study in rats with oral gavage administration on gestation days 6-19 for the prenatal teratology evaluation and on gestation day 6 through to lactation day 20 for the postnatal development evaluation. **The only statistically significant finding was a slight increase in the number of male offspring from high-dose dams with retained areolar regions at post-natal day (PND) 13 compared to offspring from control animals. However, by PND 18 the retained areolar regions were no longer present.**
repeated-dose oral toxicity in rats	28-day-day oral study in rats: NOAEL = 300 mg/kg-bw/day, based on <u>hematology</u> changes (leucocytosis) , and increased absolute and relative <u>liver</u> weights with corresponding clinical chemistry changes (decreased prothrombin time [females only], decreased total protein and increased liver enzymes) in males and females; **and increased absolute and relative <u>adrenal gland</u> weights with corresponding histopathological changes**[1] (bilateral cortical cell hypertrophy associated with vacuolation, and increased <u>bile acids</u> (9-fold or 792%) in males. 90-day oral subchronic study in rats using: No adverse effects were observed up to the highest dose of 500 mg/kg (NOAEL). Note: a study summary provided by the [redacted] submitter.	In a 28-day feeding study, rats showed changes in organ weights, clinical chemistry, hematology and histopathology at 650 mg/kg with a NOAEL of 184 mg/kg for systemic toxicity (as reported in HPV Hazard Characterization for Trimellitates category) . 90-day oral subchronic study in rats: NOAEL = 225 mg/kg based on a LOAEL of 1000 mg/kg. There were no significant changes in clinical signs, body weight and food consumption. There were minor changes in some blood chemistry parameters, together with organ weights suggesting an effect in liver. Microscopic pathology indicated changes to the liver and spleen, which could be attributed to administration of the substance; however, the changes were thought to be adaptive. Note: a study summary provided by the [redacted] submitter.

***** RAD reviewer calculated the Primary Irritation Index (PII) to be 1.67. This PII would result in the lowest classification, mild irritation, by Draize (0-2 = mild, 2-5 = moderately irritating, 5-6 = moderately to severely irritating, 6-8 = severely irritating). **Pregnant dams were administered 0 , 500 mg/kg-bw/day of the test item [redacted]) or [redacted] (positive control) by oral gavage during gestational days 12-19. RNA was isolated from fetal testes and analyzed using whole rat genome microarrays. ***pregnant rats were treated on GDs 6 to 19 at dose levels of 0, 100, 300, or 1000 mg/kg-bw/day. [1]Results of the study do not allow determining if the observed adrenal gland changes in males from the high dose group are the result of corticosteroid deficiency (disruption of the hypothalamic-pituitary-adrenocortical axis) from direct adrenocortical inhibition by the test item or if they are the result of excess ACTH secretion from the pituitary due to stress mechanisms.

- **Other Information:** (structural alert or component of interest, basis, etc.)
  - N/A

- **Point of Departure Selected and Basis:**

The concern is based on ester hydrolysis of the trimellitate moiety in the PMN. Absorption is poor and the degree of esterase cleavage of the trimellitate moiety is uncertain.

  - Reproductive effects in male rats treated with [redacted].In a combined oral reproductive/ developmental toxicity screening test (OECD 421), a NOAEL of 100 mg/kg-day was identified for reproductive toxicity in males based on the decreases in spermatocytes and spermatids in male rats at 300 and 1000 mg/kg-day(males were exposed for 46 days (including mating) and females from 14 days prior to mating through day 3 of lactation.)
  - Developmental effects NOAEL of 300 mg/kg in an oral study (specific study type unclear) on [redacted]

Focus Assessor Comment: POD of 100 mg/kg/day was used for calculating risk for the low molecular weight species. A residual of up to [redacted] was noted for [redacted] NOAEL for this is 22.5 mg/kg-bw/day Thus, risks were also run using this as well. [Note [redacted] is well absorbed by all routes so 100% absorption is assumed for all routes for this calculation.]

Exposure Routes of Interest: (Be extremely clear when excluding routes; consider potential future scenarios and if these routes can still be ruled out.

- __x_Inhalation: [Rationale if excluded]
- __x_Dermal: [Rationale if excluded]
- __x_Ingestion: [Rationale if excluded]

PART B

Focus Date: 5/11/2017

Focus Assessor: Sharon Oxendine

USES and EXPOSURES:

- **Uses:** Water-reducible resin [redacted] This is a polymer exemption (E1).

- **Worker Exposure:**
  - **Inhalation:**

    Exposure to Particulate (non-volatile)
    Potential Dose Rate: 2.2E+0 mg/day over 57 days/yr

    Exposure to Mist (non-volatile)
    Potential Dose Rate: 7.2E+1 mg/day over 14 days/yr

  - **Dermal:**

    Exposure to [redacted] concentration
    Potential Dose Rate: 1.1E+3 mg/day over 19 days/yr

    Exposure to [redacted] concentration
    Potential Dose Rate: 1.8E+3 mg/day over 19 days/yr

    Exposure to [redacted] concentration
    Potential Dose Rate: 3.2E+2 mg/day over 57 days/yr

    Exposure to [redacted] concentration
    Potential Dose Rate: 1.1E+3 mg/day over 14 days/yr

- **General Population Exposure:**
  - **Drinking Water:** ADR up to 1.14E-2 mg/kg/day
  - **Fish:** --
  - **Air/Inhalation:** ADR up to 7.69E-2 mg/kg/day (fugitive air)

- **Consumer Exposure:** N/A

RISK CALCULATIONS:

- **Worker Calculations:**

Risks were identified for workers for reproductive toxicity via dermal but not inhalation exposures when applying the analog POD to the entire PMN substance, as shown below.

Focus Worker Calculations MOE = (POD x Abs Rate) / ((PDR x Abs Rate) / BW) Acceptable MOE ≥100, 1000																		
Exposure Scenarios and Values[1]		POD= N/LOAEL (mg/kg/ day)		POD Route Absorp . Adj[2]				Potential Dose Rate (mg/day)		Exposure Route Absorp Adj[2]		Structural Alert/ Component as % of PMN		Avg BW[3] All Adults, 80 (kg)			Margin of Exposure[4] (POD/PMN Dose)	Inhalation Fold" Factor[5] (Benchmark/ MOE)
WORKER RISK																		(NOAEL=100)
Highest/Worst Case Doses from Engineering Report																		(LOAEL=1000)
Inhalation	(	100.000	x	100%	)	÷	(	7.2E+01	x	100%	x	100%	÷	80	)	=	111	0.9
Dermal	(	100.000	x	100%	)	÷	(	1.8E+03	x	15%	x	100%	÷	80	)	=	29.6296	N/A

[1] Inhalation doses in mg/day are from the Engineering Report generated using ChemSTEER. Unless otherwise stated, the assumption is an 8-hr day.The EPA/OPPT 2-Hands Dermal Contact wit[redacted] Model calculates worker dermal exposures to a [redacted]. Model assumptions are: (1) surface area of contact equals two hands (1,070 cm2); (2) high-end default value of quantity remaining on skin = 2.1 mg/cm2 (low-end default = 0.7 mg/cm2); (3) weight fraction of chemica[redacted]; (4) 1 contact/worker-day; (5) no use of controls or gloves to reduce exposure; (6) exposure duration = 1 to 4 hours based expectation that worker will, at a minimum, thoroughly wash hands at lunch or end of the day.

[2] Absorption adjustments for Focus - Assume 100% for POD; For Exposure. If risks, consider adjustments for absorption,etc.

[3] USEPA 2011. Exposure factors handbook, final report, EPA/600-R09/052F, 2011, Chapter 8 Body Weight Studies,Table 8-1, Recommended Values for Body Weight http://www.epa.gov/ncea/efh/pdfs/efh-chapter08.pdf

[4] Benchmark (Acceptable) MOEs are 100 for NOAEL-based assessment and 1000 for LOAEL-based assessment.

[5] Fold factor = value to be applied to bring INHALATION MOE up to acceptable level, used by the CEB Industrial Hygenist to determine respirator recommendations. NOAEL-based fold factor = 100/MOE; LOAEL-based fold factor = 1000/MOE.

Risk were not identified for workers for reproductive toxicity when applying the analog POD only to the [redacted], as shown below

Focus Worker Calculations MOE = (POD x Abs Rate) / ((PDR x Abs Rate) / BW) Acceptable MOE ≥100, 1000																		
Exposure Scenarios and Values[1]		POD= N/LOAEL (mg/kg/ day)		POD Route Absorp . Adj[2]				Potential Dose Rate (mg/day)		Exposure Route Absorp Adj[2]		Structural Alert/ Component as % of PMN		Avg BW[3] All Adults, 80 (kg)			Margin of Exposure[4] (POD/PMN Dose)	Inhalation Fold" Factor[5] (Benchmark/ MOE)
WORKER RISK																		(NOAEL=100)
Highest/Worst Case Doses from Engineering Report																		(LOAEL=1000)
Inhalation	(	100.000	x	100%	)	÷	(	7.2E+01	x	100%	x	22%	÷	80	)	=	505	0.2
Dermal	(	100.000	x	100%	)	÷	(	1.8E+03	x	15%	x	22%	÷	80	)	=	134.6801	N/A

[1] Inhalation doses in mg/day are from the Engineering Report generated using ChemSTEER. Unless otherwise stated, the assumption is an 8-hr day.The EPA/OPPT 2-Hands Dermal Contact with [redacted] Model calculates worker dermal exposures to a [redacted]. Model assumptions are: (1) surface area of contact equals two hands (1,070 cm2); (2) high-end default value of quantity remaining on skin = 2.1 mg/cm2 (low-end default = 0.7 mg/cm2); (3) weight fraction of chemical in liquid; (4) 1 contact/worker-day; (5) no use of controls or gloves to reduce exposure; (6) exposure duration = 1 to 4 hours based expectation that worker will, at a minimum, thoroughly wash hands at lunch or end of the day.

[2] Absorption adjustments for Focus - Assume 100% for POD; For Exposure. If risks, consider adjustments for absorption,etc.

[3] USEPA 2011. Exposure factors handbook, final report, EPA/600-R09/052F, 2011, Chapter 8 Body Weight Studies,Table 8-1, Recommended Values for Body Weight http://www.epa.gov/ncea/efh/pdfs/efh-chapter08.pdf

[4] Benchmark (Acceptable) MOEs are 100 for NOAEL-based assessment and 1000 for LOAEL-based assessment.

[5] Fold factor = value to be applied to bring INHALATION MOE up to acceptable level, used by the CEB Industrial Hygenist to determine respirator recommendations. NOAEL-based fold factor = 100/MOE; LOAEL-based fold factor = 1000/MOE.

Based on the RESIDUAL ([redacted] risks were identified for workers via dermal but not inhalation exposure (assuming 100% absorption based on [redacted] data), as shown below:

Focus Worker Calculations MOE = (POD x Abs Rate) / ((PDR x Abs Rate) / BW) Acceptable MOE ≥100

Exposure Scenarios and Values[1]	POD= NOAEL (mg/kg/ day)		POD Route Absorption Adj[2]		Potential Dose Rate (mg/day)		Exposure Route Absorption Adj[2]		Structural Alert/Component as % of PMN		Avg BW[3] All Adults, 80 (kg)		Margin of Exposure[4] (POD/PMN Dose)	"Fold" Factor[5] (Benchmark/ MOE)
Highest Values														
Inhal	23	x	100%	÷	72.0	x	100%	x	[redacted] %	÷	80	=	125.0	0.8
Derm.	23	x	100%	÷	1800	x	100%	x	[redacted] %	÷	80	=	5.00	NA

[1] Inhalation concentrations and dermal doses are from the engineering report generated using ChemSTEER. Find details about these exposures in the engineering report.

[2] Absorption adjustments for Focus - Assume 100% for oral and inhalation exposure. Dermal exposure is 100% in this case based on analog data

[3] USEPA 2011. Exposure factors handbook, final report, EPA/600-R09/052F, 2011, Chapter 8 Body Weight Studies,Table 8-1, Recommended Values for Body Weight http://www.epa.gov/ncea/efh/pdfs/efh-chapter08.pdf

[4]Benchmark (Acceptable) MOEs are 100 for NOAEL-based assessment and 1000 for LOAEL-based assessment and 1000 for an LD50-based assessment.

[5] Fold factor = value to be applied to bring INHALATION MOE up to acceptable level, used by the Industrial Hygenist to determine respirator recommendations. NOAEL-based fold factor = 100/MOE; LOAEL-based fold factor = 1000/MOE; if LD50 is used then 1000/MOE.

- **General Population Calculations:**

Risks were not identified for reproductive toxicity for the general population, as shown below:

Focus General Population and Consumer MOE Calculations
MOE = (POD x Abs Rate) / ((PDR x Abs Rate) / BW) Benchmark (acceptable) MOE ≥100 or 1000

Exposure Scenarios and Values[1]		POD= N/LOAEL (mg/kg/ day)		POD Route Absorp Adj[2]			Exposure Acute Dose Rate (mg/kg/day)		Exposure Route Absorp Adj[2]		Multiplier for Sensitive Sub-populations[4]		Structural Alert/ Component as % of PMN			Margin of Exposure (POD/PMN Dose)
GENERAL POPULATION RISK																
Highest/Worst Case Doses from Exposure Report																
Drinking Water	(	100	x	100%	)	÷	(1.14E-02	x	100%	x	1.00	x	100%	)	=	8772
Drinking Water	(	100	x	100%	)	÷	(1.14E-02	x	100%	x	4.17	x	100%	)	=	2104
Inhal. (fugitive)	(	100	x	100%	)	÷	(7.69E-02	x	100%	x	1.00	x	100%	)	=	1300

[1] General Population and Consumer ingestion Acute Dose Rates are from the Exposure Report and are generated using E-FAST which assumes a 100% absorption rate, and uses an average adult body weight of 80 kg. Consumer ADRs are generated using the Consumer Exposure Module within the E-FAST CBI version called "NCEM2" model.

[2] Absorption adjustments for Focus: Assume 100% POD; if risks, consider adjusting for absorption, etc.

[3] Benchmark (Acceptable) MOEs are 100 for NOAEL-based assessment and 1000 for LOAEL-based assessment.

[4] Multiplier based on increased drinking water consumption for infants. Multiplier would be less for older populations, so this value is worst-case.

Based on the RESIDUAL [redacted], risks were not identified for the general population via drinking water and inhalation exposure (assuming 100% absorption based on [redacted]), as shown below:

Focus General Population and Consumer MOE Calculations MOE = (POD x Abs Rate) / ((PDR x Abs Rate) / BW) Benchmark (acceptable) MOE ≥100													
Exposure Scenarios and Values[1]	**POD= LOAEL (mg/kg/ day)**		**POD Route Absorption Adj[2]**		**Acute Dose Rate (mg/kg/bw)**		**Exposure Route Absorption Adj[2]**		**Multiplier for Sensitive Subpopulations**		**Structural Alert/Component as % of PMN**		**Margin of Exposure (POD/PMN Dose)**
GENERAL POPULATION RISK													
Highest Doses													
Drinking Water	23	x	100%	÷	0.011400	x	100%	x	1.00	x	[redacted]%	=	9868
Drinking Water	23	x	100%	÷	0.011400	x	100%	x	4.17	x	[redacted]%		2367
Inhalation	23	x	100%	÷	0.076900	x	100%	x	1.00	x	[redacted]%	=	1463

[1] General Population and Consumer ingestion Acute Dose Rates are from the exposure report and are generated using E-FAST which assumes a 100% absorption rate. See the exposure report for details about generation of exposure and body weight used.
[2] Absorption adjustments: Assume 100% based on good absorption all routes
[3] Benchmark (Acceptable) MOEs are 100 for NOAEL-based assessment and 1000 for LOAEL-based assessment and 1000 for an LD50-based assessment.

- **Consumer Calculations: N/A**